II. Remarks

A. Status of the Claims

Claims 1, 3, 8-10, 12-27, 29-32, and 35-47 are currently pending.

Claims 1, 22-26, 31, 41, and 42 were amended to correct typographical errors and for clarity. It is respectfully submitted that no new matter was added by virtue of these amendments.

B. Claim Rejection Under 35 U.S.C. § 103(a)

Claims 1, 3, 8-10, 12-27, 29-32, and 35-47 were rejected under 35 U.S.C. § 103(a) over the combination of Nutt et al. (Clinical Pharmacology and Therapeutics, Vol. 15, Number 2, pp. 156-166), Mayer et al. (U.S. 5,556,838), Ockert (U.S. 5,376,662), and European Patent No. 0 193 355. The Examiner states on page 2 of the Office Action that the rejection is "for the reasons set forth on pages 2-5 of the office action of May 26, 2009."

The rejection is respectfully traversed.

Applicants respectfully submit that the rejection over these references made in the Office Action of May 26, 2009, has been overcome by the arguments presented in the response filed on November 23, 2009.

As stated in the response filed on November 23, 2009, independent claims 1 and 41 are directed, in part, to an oral dosage form comprising a combination of an opioid

agonist, acetaminophen and an opioid antagonist, wherein a **ratio** of the opioid antagonist to the opioid agonist to the acetaminophen is such that

(i) the combination is analgesically effective when it is administered orally,

(ii) it is aversive in physically dependent human subjects when administered orally; and

(iii) it maintains an analgesic effect but does not increase analgesic efficacy of the opioid agonist together with the acetaminophen, relative to when the opioid agonist and the acetaminophen are administered orally without said opioid antagonist.

Applicants respectfully reiterate that the combination of the cited references does not teach or suggest the ratios recited in the claims 1 and 41, and therefore submit that a *prima facie* case of obviousness has not been established.

Applicants further submit that a *prima facie* case of obviousness has not been established because the Examiner has not articulated a reason that would have prompted one skilled in the art to combine the individual components of the cited references in the manner suggested by the Examiner so as to formulate the dosage form of independent claim 1 or independent claim 41.

In response to the Examiner's statement on page 3 of the Office Action of May 26, 2009, that "[t]he primary reference teaches that the mixture has significantly less miotic, behavioral and subjective effect than methadone alone," Applicants note that the portion of Nut et al. believed to be relied upon by the Examiner states:

> **By the parenteral route**, the mixtures have significantly less miotic, behavioral, and subjective effects than methadone alone …

Nutt, Abstract (emphasis added).

Applicants respectfully submit that Nut's statement on page 165, right column, first full paragraph, that "... by the oral route ...[the methadone-naloxone mixture described therein] ... is **indistinguishable** from methadone alone" (emphasis added) (alone or in combination with the cited references) would not have motivated the skilled person to formulate an oral dosage form which "is **aversive** in physically dependent human subjects when administered **orally,**" as recited in independent claims 1 and 41.

In response to the Examiner's reliance on Mayer et al., Applicants note that Mayer is directed in part to "a method of **alleviating** withdrawal symptoms in a mammal" (column 2, lines 23-33). Mayer states, e.g., that naloxone (an opioid antagonist) produces withdrawal symptoms (column 7, lines 23-26). Applicants therefore submit that Mayer (alone or in combination with the cited references) would not have motivated the skilled person to formulate an oral dosage form comprising "an opioid antagonist, and which "is aversive in physically dependent human subjects when administered orally" as recited in independent claims 1 and 41.

In response to the Examiner's reliance on the Ockert reference, Applicants note that Ockert is directed in part to "local administration of naloxone at or near the nerve trauma site" (column 2 lines 35-48). Ockert states in part that "[n]aloxone and other opiate-antagonists competitively **antagonize** both exogenous opiates (such as heroine or morphine) and endogenous opioids (such as B-endorphin, enkephalins, and dynorphin at both peripheral and central nerve opiate receptors)." Column 4, lines 8-12. Applicants therefore submit that Ockert (alone or in combination with the cited references) would not have motivated the skilled person to combine an opioid agonist and an opioid antagonist in a dosage form which "is aversive in physically dependent human subjects when administered orally" as recited in independent claims 1 and 41.

For the foregoing reasons, Applicants submit that a dosage form comprising the combination of an opioid agonist, acetaminophen and an opioid antagonist recited in independent claims 1 and 41 would not have been obvious in view of the combination of the cited references.

With further regard to new claims 46 and 47, Applicants submit that the combination of the cited references would not have taught or suggested a dosage form "consisting of the opioid agonist, the acetaminophen, the opioid antagonist, and one or more pharmaceutically acceptable inert excipients." This is because fluoxetine, norfluoxetene or salts thereof of European patent No. 0 193 355 and the NMDA receptor blockers of Mayer are excluded from such dosage form by virtue of the "consisting of" language.

Withdrawal of the rejection is respectfully requested.

B. Double Patenting

Claims 1, 3, 8-10, 12-27, 29-32, and 35-47 were rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-27 of U.S. Patent No. 7,419,686 in view of European Patent Application No. 0 13 355.

Claims 1, 3, 8-10, 12-27, 29-32, and 35-47 were rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-21 of U.S. Patent No. 7,172,767 in view of European Patent Application No. 0 13 355.

Claims 1, 3, 8-10, 12-27, 29-32, and 35-47 were rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-29 and 59-63 of U.S. Patent No. 6,696,066 in view of European Patent Application No. 0 13 355.

Claims 1, 3, 8-10, 12-27, 29-32, and 35-47 were rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-23 of U.S. Patent No. 6,475,494 in view of European Patent Application No. 0 13 355.

Claims 1, 3, 8-10, 12-27, 29-32, and 35-47 were rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-25 and 50 of U.S. Patent No. 6,277,384 in view of European Patent Application No. 0 13 355.

Claims 1, 3, 8-10, 12-27, 29-32, and 35-47 were rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-21 of U.S. Patent No. 6,375,957 in view of European Patent Application No. 0 13 355.

Applicants acknowledge these double patenting rejections, but respectfully request that the requirement to file terminal disclaimers to obviate these rejections be held in abeyance until such time as claims are otherwise held to be allowable.

III. Conclusion

An early and favorable action on the merits is earnestly solicited. According to currently recommended Patent Office policy, the Examiner is specifically authorized to contact the undersigned by telephone in the event that a telephonic interview will advance the prosecution of this application.

Respectfully submitted,
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